REMARKS

Claims 1-26 are pending in the application. Claims 1-21 have been indicated to be in condition for allowance. Claims 22-26 are at issue. No new matter has been introduced by way of this amendment.

Preliminarily, Applicants note with appreciation the withdrawal of the finality of the previous Office Action as well as the withdrawal of the prior rejections under 35 U.S.C. § 112 and for double patenting.

I. The specification does not contain new matter.

The Examiner objects to the specification as allegedly containing new matter. Applicants disagree. Nonetheless, to advance the prosecution of the case, the language at issue has been omitted from the specification. Accordingly, Applicants request withdrawal of the objection.

Additionally, the benefit of priority of the parent applications, U.S. Application Serial No. 08/422,436 and U.S. Application Serial No. 08/851,162, was asserted in the transmittal letter accompanying the present application at the time of filing. *See* Transmittal Letter filed July 12, 2000 by Fish & Richardson, P.C. at page 2. The cross-reference to related applications, however, was not made until Applicants' submission of April 24, 2002. A petition to accept the unintentionally delayed claim of the benefit of priority of the parent applications is submitted herewith, accompanied by the appropriate fee under 37 C.F.R. § 1.17 (t) and a statement that the entire delay between the date the claim for priority was due under 37 C.F.R. § 1.78 (a) (2) and the date the claim was made was unintentional. Applicants respectfully request acceptance of the petition and grant of the request.

II. Claims 22-26 are patentable over the cited references.

Claims 22-26 are rejected under 35 U.S.C. § 103 for alleged obviousness in view of Chang et al., Hart et al., and Holtz et al. Applicants traverse.

Claims 22-26 recite methods for refolding an insulin-like growth factor-I (IGF-I) polypeptide derived from a yeast cell medium to yield an authentic, properly folded IGF-I polypeptide comprising denaturing and renaturing IGF-I species present in an IGF-I mixture from the yeast cell medium using an unfolding/refolding buffer

comprising urea, dithiothreitol, alcohol, and salt, in sufficient amounts, and under conditions that allow for the reduction and subsequent oxidation of disulfide bonds, thereby producing an authentic, properly folded IGF-I polypeptide.

To establish a *prima facie* case of obviousness, three requirements must be satisfied: first there must be some suggestion or motivation to modify the reference or to combine the reference teachings; second, there must be a reasonable expectation of success for achieving the claimed invention and its particular results; and, third, the prior art references must teach or suggest all the claim limitations. *See In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

The instant record fails to establish sufficient motivation to combine Chang et al., Hart et al., and Holtz et al. The importance of the requirement of a motivation to combine prior art references was recently explained by the Federal Circuit as follows:

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness.... "The factual inquiry whether to combine references must be thorough and searching." It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

In re Lee, 277 F.3d 1338 (Fed. Cir. 2002) (citations omitted).

Moreover, a prior art reference must be considered in its entirety, including disclosures that would teach away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Applicants assert that there is no motivation to combine Chang et al., Hart et al., and Holtz et al. Holtz et al. describes a method for purifying correctly folded, soluble IGF-I recombinantly produced from *P. pastoris* culture medium. The Examiner seems to have overlooked the reasoning for the first cation exchange wash system of Holtz et al. Holtz et al. specifically call for the removal of aberrant forms of IGF-I from the matrix, including multimeric and misfolded monomeric forms of IGF-I. *See, e.g.*, Holtz et al., column 2, lines 15-43. The mere description of multimeric and misfolded monomeric forms of IGF-I as aberrant by Holtz et al. must be accepted by the Examiner as an indication that Holtz et al. did not want these

forms maintained in the column. Applicants' disclosure of an "unfolding/refolding step" in their process is principally beneficial with respect to the multimeric and misfolded IGF-I which Applicants seek to maintain and which Holtz et al. seek to remove. Accordingly, there is no motivation to add an unfolding/refolding step as described by Chang et al. and Hart et al. to the method of Holtz et al.

Additionally, both Chang et al. and Hart et al. describe methods for refolding insoluble, misfolded IGF-I specifically resulting from recombinant production in *E. coli* and isolation from inclusion bodies of cell lysate. Note that the issue addressed by Chang et al. is focused on problems resulting from the type of host utilized. *See, e.g.,* Chang et al., column 1, lines 40-61 (describing prokaryotic cells as host cells that express recombinant IGF-I abundantly in the form of inclusion bodies). Applicants submit that Chang et al., which focus on a problem unique to a particular host system, does not lend itself to the proposed combination of references. The Examiner, however, asserts that the motivation to combine the cited references is provided by Chang et al. because Chang et al. teach the importance of correctly folded IGF-I for biological activity. Applicants assert that the importance of retaining biological activity for any recombinant protein is reference-independent. Rather, Chang et al. teach the importance of overcoming a specific limitation of prokaryotic host systems, i.e., inclusion bodies. This is not a problem addressed by Holtz et al.

Moreover, Chang et al. teach away from a combination with Hart et al. Hart et al. describe a multi-step approach in which IGF-I recovered from *E. coli* and reduced and denatured with urea and dithiothreitol (DTT) is refolded in a refolding buffer. *See* Hart et al. at 218. Hart et al. does not teach a method for effecting both unfolding and refolding in a single buffer. Chang et al., however, teach away from a multi-step approach to unfolding and refolding of IGF-I. *See, e.g.,* Chang et al. at column 3, lines 47-48 ("The multiple steps required to achieve correct folding are time-consuming."); column 6, lines 22-25 ("There is a need in the art for a simple, *one-step*, efficient protocol for refolding insoluble, misfolded IGF-I into the correct conformation so that the biological activity of the IGF-I can be restored."); column 6, lines 61-64. Accordingly, Chang et al. teach away from a combination with Hart et al.

Hart et al. also teach away from a combination with Chang et al. Hart et al. teach that the properties of solvent have a large effect on IGF-I refolding. Hart et al. propose that the forces governing the selectivity of IGF-I refolding are forces

governing non-covalent folding of the polypeptide, not the energies of disulfide bond formation. Hart et al. state that disulfide bond formation does not determine the pathway for polypeptide folding. *See* Hart et al. at 228. Accordingly, Hart et al. teach away from a combination with Chang et al., wherein it is taught that proper IGF-I refolding is dependent upon proper disulfide bond formation. *See, e.g.*, Chang et al. at column 2, lines 3-15; column 6, lines 58-61. Thus, there is no motivation to include DTT, a reducing agent of disulfide bonds, as taught by Chang et al., in the refolding buffer of Hart et al.

Moreover, Applicants assert that there is no reasonable expectation of success in the proposed combination of the methods of refolding *E. coli* proteins of Chang et al. and Hart et al. with the method of purifying a yeast protein of Holtz et al. The source of the protein to be folded impacts the effectiveness of the folding method used. *E. coli* lacks eukaryotic glycosylation systems, while yeast can post-translationally modify proteins. Thus, production of IGF-I in yeast results in different IGF-I variants than those recombinantly produced in *E. coli*. Accordingly, one having ordinary skill in the art would expect yeast IGF-I to react differently than IGF-I produced in *E. coli*.

Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

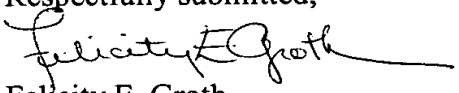
In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please contact the undersigned at 215-557-5908.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Date: January 29, 2003

Respectfully submitted,



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Attachments

Version with Markings to Show Changes Made
Petition to Accept Claim of Unintentional Delay
Fee
Supplemental Declaration and Power of Attorney

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the application as follows:

IN THE SPECIFICATION:

At page 1, after the title, please amend the first paragraph to read as follows:

--CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. Serial No. 08/851,162 filed May 5, 1997, which is a divisional of U.S. Serial No. 08/422,436 filed April 14, 1995[, each of which is incorporated herein by reference in its entirety].--